II. REMARKS

A. Status of the Claims

This is in Response to the Final Office Action dated May 11, 2010. A petition for three-month extension of time, a Request for Continued Examination and the corresponding fees accompany this Amendment.

Claim 9 has been amended to remove the language "which is not expressed in normal liver". Claims 33 and 39 have been amended to recite "mouse" in place of "mammal except human". As stated by the Examiner on page 14 of the Office Action, support for mice can be found in Example 2 and 4 of the Specification. Claims 30 and 36 have been amended to add that the antibodies are humanized. Support for this amendment can be found in the present Specification as filed, for example, from page 16, line 1 to page 20, line 20 and Example 4, as well as in the sequence listing.

New claims 42 and 43 have been added. Both of these claims recite "wherein the mRNA expression of the peptide is higher in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue." Support for this phrase can be found in pages 42-43 of the specification as filed under the subtitle of "Expression Analysis of human GPC3 mRNA using GeneChip." Claim 42 also recites "wherein the isolated monoclonal antibody detects cancer when exposed to cancer cells" and claim 43 recites wherein the isolated monoclonal antibody is used in the treatment of cancer. Support for this phrase can be found e.g. in the first two paragraphs in the Disclosure of the Invention found on pages 2-3 of the specification

New claims 44 and 45 have also been added. These claims are the similar to amended claims 30 and 36, with the difference that the term "humanized" has been changed to "chimeric" in claims 44 and 45. Support for these new claims can be found in the present Specification as filed, for example, from page 16, line 1 to page 20, line 20 and Example 4, as well as in the sequence listing.

Claims 1-8 and 10-24 were previously canceled without prejudice.

After claim amendments and additions herein, claims 9 and 25-45 will be pending in this application.

It is respectfully submitted that no new matter is being introduced in this amendment.

B. Claim Rejections- 35 U.S.C. § 103

1. In the Office Action mailed on May 11, 2010, the rejection of claims 9 and 23 to 29 under 35 U.S.C. § 103(a) as being obvious over Lage et al. (Virchows Arch 2001 438:567-573), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) was maintained.

Claim 9 as amended reads:

> An isolated monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC 3 as set forth in SEQ ID NO: 4, wherein the antibody has ADCC or CDC activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells.

New claims 42 and 43 read as follows:

> 42. The isolated monoclonal antibody of claim 1, wherein the mRNA expression of the peptide is higher in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue and wherein the isolated monoclonal antibody detects cancer when exposed to cancer cells.
>
> 43. The isolated monoclonal antibody of claim 1, wherein the mRNA expression of the peptide is higher in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue and wherein the isolated monoclonal antibody is used in the treatment of cancer.

One of skill reviewing the Lage reference would understand that the Be-F4 antibody disclosed in the Lage reference binds more tightly to normal liver tissue than liver cancer cells. More specifically, the Lage reference discloses a monoclonal mouse antibody, Be-F4, which was generated by means of immunization with a synthetic oligopeptide consisting of the amino acid residues 537-556, representing a putative hydrophilic domain of the Glypican 3 core polypeptide (See Lage et al., second paragraph of the left column of pg. 568). IHC analysis demonstrates that the expression level of the protein recognized by Be-F4 is more pronounced in the atypical multidrug-resistant gastric carcinoma cell line EPG85-257RNOV than in the non-resistant parental line EPG85-257P. This observation is in accordance with the results of Northern blot analyses, detecting GPC3 mRNA expression level in those cell lines (See Lage et al., the right column of p. 570). However, HCC cells constantly showed a decreased staining intensity by Be-F4 when compared with the staining signal obtained in non-cancerous liver cells from the same section. Be-F4-specific staining signal was completely absent in 28% of poorly differentiated G3 tumors and 5.6% of moderately differentiated HCC cases (See Lage et al., the first paragraph of the right column of p. 572). A person skilled in the art could not predict from the disclosure of Lage that glypican may represent a target for antibody therapy, nor even expected whether the glypican 3 protein is expressed in a HCC cell.

As pointed out in the § MPEP 2145 (X)(a): "[a]ny judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin,* 443 F.2d 1392, 1395, 170 U.S.P.Q. 209, 212 (CCPA 1971). It is only from review of Applicant's disclosure that one of skill would understand that an isolated monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC 3 could result in an antibody having ADCC or CDC activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells.

Further, with regard to new cells 42 and 43 it is only from review of Applicant's disclosure that one of skill would know that an isolated monoclonal antibody against a peptide

consisting of amino acid residues 375-580 of GPC 3 could have mRNA expression of the peptide higher in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue. One of skill in the art reviewing Lage would have expected the mRNA expression of the peptide to be lower in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue. As the Examiner relies on knowledge gleaned only from Applicant's disclosure, the rejection is improper.

In the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody of Lage et al. using the methods of Steplewski et al., in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

Even if, as asserted by the Examiner, Steplewski et al. teach that humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes, and Dillman et al. teach that humanized antibodies exhibit complement-mediated cytotoxicity, one of skill would have had no motivation to humanize the monoclonal antibody disclosed in the Lage reference. One of skill would not have known from the Lage reference that GPC3 is more highly expressed in HCC than in normal liver tissue as the Lage reference teaches that an antibody to GPC3 would bind more tightly to normal liver tissue than to hepatic cancer cells. One of skill in the art clearly would not be motivated to obtain a humanized antibody having desired properties to meet the goal of developing a new cancer therapy or marker with a reasonable expectation of success by effecting humanized modification starting from the Be-F4 antibody having such a binding property.

In order to further distinguish over the Lage reference, Applicants have added new claims 42 and 43. These claims both add the feature that "the mRNA expression of the peptide is higher in hepatoma lesions than the mRNA expression of the peptide in normal liver tissue" and respectively recite that the isolated monoclonal antibody detects cancer when exposed to cancer cells and that the isolated monoclonal antibody is used in the treatment of cancer. As explained above, the Lage reference teaches that HCC cells constantly showed a decreased staining intensity by Be-F4 when compared with the staining signal obtained in non-cancerous liver cells

from the same section. In view of this teaching, one of skill in the art would not expect that an antibody to GPC3 would be useful in either detection or treatment of cancer.

In addition, and as explained in Applicants' previous response, the disclosure of Dillman et al. merely provides general guidance concerning humanized antibodies, not a clear teaching or implication to direct someone toward the features of the presently claimed invention. Mast et al. and Midorikawa et al. also do not provide clear teaching or implication about the features of the presently claimed invention, specifically an "antibody against a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEQ ID NO:4" as recited in claim 9 of the present invention.

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 § U.S.C. 103(a) is respectfully requested. In addition, Applicants respectfully submit that new claims 42 and 43 are patentable over the cited references.

2. In the Office Action mailed on September 1, 2009, the rejection of claims 9 and 23 to 29 under 35 U.S.C. § 103(a) as being obvious over Filmus et al. (U.S. Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85:4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327:577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) were maintained.

In the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody 1G12 disclosed in Filmus et al. using the methods of Steplewski et al, in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

Claim 9 requires the antibody have ADCC or CDC activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells. New claims 42 and 43 require the mRNA expression of the peptide to be higher in hepatoma lesions than the

mRNA expression of the peptide in normal liver tissue and also respectively require the isolated monoclonal antibody detects cancer when exposed to cancer cells and the isolated monoclonal antibody is used in the treatment of cancer. As previously explained to the Examiner and as also acknowledged by the Examiner, the Filmus reference does not teach or suggest a cytotoxic activity for a monoclonal antibody to GPC3. Further, it was well known in the art that the 1G12 antibody disclosed in Filmus et al. did not exhibit cytotoxicity (e.g., ADCC activity and CDC activity) in unconjugated form. Accordingly, a person skilled in the art reviewing the disclosure of the Filmus reference would have no reason to expect that a monoclonal antibody to GPC3 would have ADCC activity or CDC, even in view of Steplewski et al, further in view of Dillman et al., further in view of Mast et al. and Midorikawa et al.

It is only using knowledge gleaned only from applicant's disclosure that the Examiner is able to assert that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody 1G12 disclosed in Filmus et al. using the methods of Steplewski et al. Such use of hindsight reconstruction is improper. *In re McLaughlin,* 443 F.2d 1392, 1395, 170 U.S.P.Q. 209, 212 (CCPA 1971).

For the foregoing reasons, withdrawal of the rejection of claims 9 and 23 to 29 under 35 U.S.C. § 103(a) as being obvious over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85:4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327:577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) is respectfully requested. Applicants also respectfully submit that new claims 42 and 43 are patentable over the cited references.

C. Double Patenting Rejections

In the Office Action, claims 9 and 23 to 29 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 6, 7, 16, 21, 22, 29, 32, 34, 38, 39, 41, and 43 to 50 over copending U.S. Patent Application No. 10/583,795.

Applicants again acknowledge the rejection and submit that filing of a terminal disclaimer will be considered upon indication that the current claims or the pending claims of U.S. Patent Application No. 10/583,795 are otherwise allowable.

D. Written Description Rejections

Claims 9 and 25-41 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

With regard to claim 9, the Examiner objected to the wording "which is not expressed in normal liver". This language has been removed from claim 9 and as a result, the rejection is moot.

With regard to the Examiner's objection to claims 30-41, the Examiner states that support exists for humanized antibodies and chimeric antibodies comprising the CDR1, CDR2, and CDR3 of the H chain variable region as set forth in SEQ ID NO: 10 and the CDR1, CDR2 and CDR3 of the L chain variable region as set forth in SEQ ID NO: 1 or humanized antibodies and chimeric antibodies comprising the CDR1, CDR2 and CDR3 of the H chain variable region as set forth in SEQ ID NO: 12 and the CDR1, CDR2 and CDR2 of the L chain variable region as set forth in SEQ ID NO: 30 but argues that it does not (sic) support the broadly claimed antibodies of claim 30 and 36 which the Examiner asserts encompasses a broader gunus of any type of antibody according to claim 9 comprising the recited CDRS. To expedite prosecution, Applicants have amended claims 30 and 36 to add the term "humanized" and have added new claims 44 and 45 which are identical to amended claims 30 and 36 except that "chimeric" is substituted for the term "humanized.

The Examiner also objected to claims 33 and 39, contending that the variable region comprising the CDRs of SEQ ID NOs 10/18 and 12/20 are from mice not just any mammal. Again, for the purposes of expediting prosecution of the present application, Applicants have amended these claims to recite "the antibody of a mouse" in place of the language "antibody of a mammal except human".

In view of the above, Applicants respectfully request that the rejection of Claims 9 and 25-41 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement be withdrawn.

E. Conclusion

Reconsideration of the present application is respectfully requested. If the Examiner has any questions or concerns regarding this response and amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number set forth below.

This Request for Continued Examination and Amendment is being submitted in response to the final Office Action dated May 11, 2010 in the above-identified application. A Notice of Appeal was filed on October 12, 2010 and therefore it is believed that no fee is due at this time. If it is determined that any additional fee is due in connection with this filing, the Commissioner is authorized to charge said fees to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly requested.

Respectfully submitted,
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